Critical Care

REVIEW

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Septic shock in the immunocompromised cancer patient: a narrative review

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Abstract

Immunosuppressed patients, particularly those with cancer, represent a momentous and increasing portion of the population, especially as cancer incidence rises with population growth and aging. These patients are at a heightened risk of developing severe infections, including sepsis and septic shock, due to multiple immunologic defects such as neutropenia, lymphopenia, and T and B-cell impairment. The diverse and complex nature of these immunologic profiles, compounded by the concomitant use of immunosuppressive therapies (e.g., corticosteroids, cytotoxic drugs, and immunotherapy), superimposed by the breakage of natural protective barriers (e.g., mucosal damage, chronic indwelling catheters, and alterations of anatomical structures), increases the risk of various infections. These and other conditions that mimic sepsis pose substantial diagnostic and therapeutic challenges. Factors that elevate the risk of progression to septic shock in these patients include advanced age, pre-existing comorbidities, frailty, type of cancer, the severity of immunosuppression, hypoalbuminemia, hypophosphatemia, Gram-negative bacteremia, and type and timing of responses to initial treatment. The management of vulnerable cancer patients with sepsis or septic shock varies due to biased clinical practices that may result in delayed access to intensive care and worse outcomes. While septic shock is typically associated with poor outcomes in patients with malignancies, survival has significantly improved over time. Therefore, understanding and addressing the unique needs of cancer patients through a new paradigm, which includes the integration of innovative technologies into our healthcare system (e.g., wireless technologies, medical informatics, precision medicine), targeted management strategies, and robust clinical practices, including early identification and diagnosis, coupled with prompt admission to high-level care facilities that promote a multidisciplinary approach, is crucial for improving their prognosis and overall survival rates.

Keywords Septic shock, Immunocompromised host, Neoplasms, Hematologic neoplasms, Hematopoietic stem cell transplantation, Organ transplantation, Critical care, Critical care outcomes

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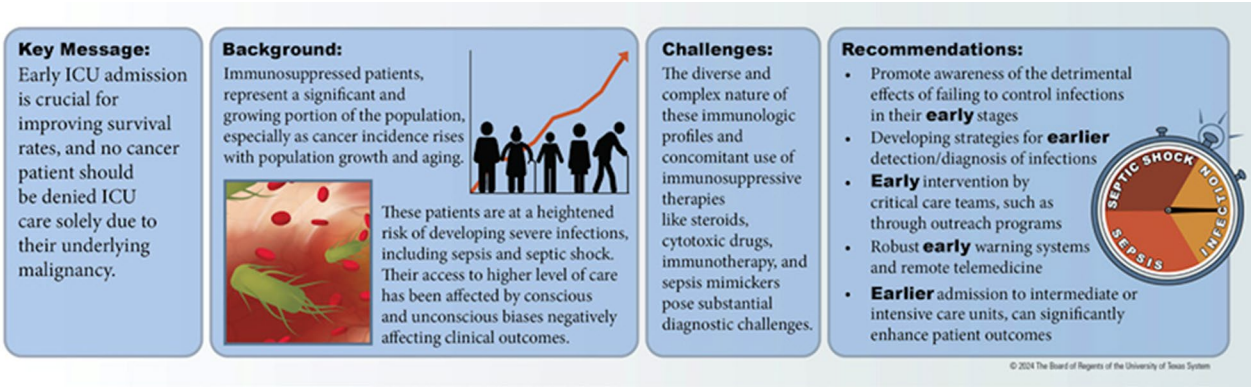
Graphical abstract


Key Message:
Early ICU admission is crucial for improving survival rates, and no cancer patient should be denied ICU care solely due to their underlying malignancy.
Background:
Immunosuppressed patients, represent a significant and growing portion of the population, especially as cancer incidence rises with population growth and aging.
These patients are at a heightened risk of developing severe infections, including sepsis and septic shock. Their access to higher level of care has been affected by conscious and unconscious biases negatively affecting clinical outcomes.
Challenges:
The diverse and complex nature of these immunologic profiles and concomitant use of immunosuppressive therapies like steroids, cytotoxic drugs, immunotherapy, and sepsis mimickers pose substantial diagnostic challenges.
Recommendations:
Promote awareness of the detrimental effects of failing to control infections in their early stages
Developing strategies for earlier detection/diagnosis of infections
Early intervention by critical care teams, such as through outreach programs
Robust early warning systems and remote telemedicine
Earlier admission to intermediate or intensive care units, can significantly enhance patient outcomes
SEPTIC SHOCK
NON-INFECTIOUS
SEPSIS

Introduction

Acquired immunosuppression usually affects patients with all type of malignancies, stem cells and solid organ transplantation, those receiving immunosuppressive therapies, human immunodeficiency virus infection, and others. The 2021 annual US National Health Interview Survey showed that 6.6% of adults had an immunosuppressive condition or were taking immunosuppressive medications [1]. The approach and management of the immunocompromised cancer patient with septic shock may be different from that of the immunocompetent patient because of the underlying disease, the type and degree of immunosuppression, the stage and severity of the underlying condition, comorbidities, and therapies associated with high toxicity [2, 3].

Immunocompromised hosts, especially those with cancer, have suffered from unconscious and conscious biases, including Intensive Care Unit (ICU) admission denials, delayed ICU admissions, time-limited ICU trials, and palliative ICU admissions [4]. In the late 1990s international guidelines, patients with malignancies had a lower priority for admission to the ICU [5]. The most recent guidelines for ICU admission, discharge, and triage, published in 2016 have addressed those issues, but differences persist [6]. While most of the Surviving Sepsis Campaign guidelines may apply to this population, gaps in knowledge still exist [7]. Therefore, there is a critical and unmet need for a better understanding of the unique challenges these patients offer regarding early recognition, differential diagnosis, and timely interventions. The purpose of this article is to review the current understanding, highlight the current and persistent issues, and propose a new paradigm to improve the outcomes of septic shock in cancer patients, those with solid tumors, hemato-oncologic malignancies, and hematopoietic stem cell transplantation (HSCT). The methodology for this narrative review involved a comprehensive and systematic search of the literature, guided by the expertise of an international panel of experts. The panel of experts collectively identified key topics, selected relevant studies, and synthesized findings to provide a thorough overview of current knowledge. Regular consensus consultations ensured the integration of diverse perspectives and the accuracy of the conclusions drawn.

Epidemiology

The incidence of cancer is increasing; the risk of developing sepsis is also on the rise despite a reduction in mortality. The risk of developing sepsis is ten times higher in cancer patients [8]. Given the world's continuously growing population, currently surpassing eight billion, and the increased cancer survival rates, the number of individuals at augmented risk will rise [9–14]. In 2022, there were 19.98 million new cases and 9.74 million deaths globally, resulting in approximately 53.5 million prevalent cases over five years [15–17]. Since 1991, smoking reduction, better screening, and novel cancer therapies contributed to the 33% decline in cancer mortality in the USA [16].

Patients with cancers have higher morbidity than non-cancer patients, higher risk of infection, higher emergency room visits and higher rate of admission. A large epidemiological study of emergency services utilization in the USA (2006–2012) found that four million (4.2%) annual adult emergency room (ER) visits involved cancer diagnoses [18]. Sixty percent of cancer patients admitted to the hospital in the USA (2006–2012) had primarily severe infections or cardiorespiratory failure, compared to 16% of non-cancer patients. A smaller study also reported that cancer patients had a higher admission rate than non-cancer patients (47.6% vs. 13.6%) [19]. In the

study by Rivera et al., the most common causes of infections were pneumonia, urinary tract infections, and septicemia [18]. In the study by Legrand et al., the four most frequent sources of infections were pneumonia (70.2%), abdomen (19.1%), skin and soft tissue infection (4.3%) and catheter-related infection (2.8%) [20]. Factors associated with higher hospitalization rates included male sex, older age, comorbidities, and lung cancer. Another study at a Comprehensive Cancer Center reported 387,306 adult cancer admissions in a 20-year period, of which 40.4% were surgical patients, 28.2% had hematologic malignancies, and 31.4% solid tumors [21]. Among these, 12.9% went to the ICU; 38.4% of those who died at discharge had infections as principal diagnosis (e.g., sepsis, pneumonia).

Although less often reported, data on cancer patients with sepsis are also available. Between 1979 and 2001, among 854 million patients hospitalized in the USA, 1.78 million patients had cancer and sepsis, equating to 1,465 sepsis cases per 100,000 cancer patients in the USA [15]. A 2011 state-wide (population 25.65 million) study of 2,713,776 hospital discharges found that 303,492 (14%) had cancer and 17,523 (5.8%) of them also had sepsis [22]. Similarly, a study of 2,901,019 patients in 409 US hospitals (2009–2014) reported a 6% sepsis occurrence and 15% overall mortality [23]. Another large study using the US National Readmission Database, encompassing over twenty-seven million hospitalizations, found that 4% of patients had sepsis, 15.1% had cancer, and 234,641 (5.7%) had both cancer and sepsis [2]. In the EPISEPSIS study of 206 French ICUs, 12.8% of severe sepsis admissions had metastatic cancer (7.5%) or hematological malignancies (5.3%) [24]. The global EPIC II study involving 13,796 ICU patients (51% infected) found that 17% had cancer (15.1% solid tumors, 2% hematological malignancies) [25]. Among these, infection rates were 74% for hematological patients, and 53.2% for those with solid tumors. The follow-up EPIC III study included 15,202 ICU patients, 16.7% of them had cancer (2.8% of those hematological) [26]. Similarly, 72.47% of the hematological patients and 49.85% of the solid tumor patients had an infection. Considering that, worldwide, not all cancers patients with sepsis are hospitalized, among those hospitalized, the review of three different studies performed at a high-volume cancer center demonstrated a 0.94% incidence of septic shock in solid and hematologic malignancies combined (1.68% including those not meeting Sepsis-3 criteria), and 1.44% in HSCT patients [27–29]. More recently, Liu et al. analyzed data from the National Inpatient Sample Database and found that among fourteen million patients hospitalized with sepsis between 2006 and 2014, the annual incidence rate increased at a higher rate in cancer patients [30]. They reported an increase in the annual incidence of 15.8% for Gram-negative bacteria (GNB), 7.4% for Gram-positive bacteria (GPB), 16.5% for anaerobes, and 11.6% for fungi. Whether or not those data reflect a real increase in incidence or better identification remains unclear.

Pathophysiology

Although not all cancer patients are immunosuppressed, the degree of immunosuppression is a crucial risk for sepsis and poor outcomes. The pathogenesis of sepsis is complex and depends on the type of infection and the host response involving the activation of the endothelium and complement, microvascular and coagulation dysfunction, and microbiome dysbiosis among others [31–34]. In cancer patients with sepsis, mortality and other complications are higher than in the general population, because of their intrinsic vulnerabilities and risk factors (Table 1). The affected pathways will influence development, progression and potentially outcome of sepsis.

The immune system includes rapid response, low-specificity innate immune system (complement system, phagocytic cells) and delayed response, high specificity adaptive immune system (B- and T-lymphocytes). Immunosuppression can come from the cancer, its therapy or both, Infection risks vary based on the immune defect type: for example, complement defects or inhibition (e.g., eculizumab, a C5 inhibitor) increase susceptibility to *Neisseria* and blood-borne pathogens, while defects in cell-mediated immunity increase the risk of opportunistic infections [35] (Table 2). The underlying immune status impacts the course of septic shock and the susceptibility to ICU-acquired complications [36]. The pathophysiology of cancer patients with sepsis is intertwined: both entities share common characteristics that result from a dysregulated immune system, raising the specter of their mutual impact on each other's course [37]. Few studies compare sepsis pathophysiology between immunocompromised hosts and those who are not, with various findings not always aligned with outcomes [38]. This may be because endotoxin effects are lymphocyte-independent, as shown in animal models, or because septic shock can induce acquired immunosuppression in previously non-immunosuppressed patients [34, 39]. Comorbidities such as diabetes are not only a risk factor for infection and sepsis but also a risk factor of poor outcome [40]. Advanced age, malnutrition and frailty are also well-established risk factors of poor prognosis, due to a weakened immune response and diminished physiological reserve [41].

Cancer patients, especially those with hematological malignancies, exhibit immune defects such as cytopenias, T-cell and B-cell suppression, and asplenia, all increasing the risk of sepsis and septic shock [42, 43].

Table 1 Risk factors and comparative outcomes in cancer patients with sepsis

Risk factor	Description	Impact on clinical outcomes
Severity of immunosuppression	Low levels of cluster of differentiation 4 (CD4) cells or intensive immunosuppressive treatments	Increased mortality rates
Comorbidities	Conditions such as diabetes and chronic obstructive pulmonary disease	Increased incidence of complications and mortality
Age	Advanced age of the patient	Higher mortality rates due to weakened immune response and diminished physiological reserve
Neutropenia	Common in cancer patients and those undergoing chemotherapy	Major risk factor for sepsis development and adverse clinical outcomes
Organ dysfunction	Measured by the Sequential Organ Failure Assessment (SOFA) scores	Strong correlation with mortality
Epithelial barrier dysfunction	Facilitates bacterial translocation	Risk factor for sepsis development
Immunosuppressive drugs use	Includes corticosteroids and biologic agents	Increased risk of sepsis and adverse outcomes
Renal dysfunction	Need for renal replacement therapy	Essential management to reduce mortality
Intestinal dysfunction	Increased intestinal permeability and microbial dysbiosis	Contributes to sepsis progression
Patient group	**Hospital mortality rate (%)**	**Adverse events**
General immunocompromised patients	64.9–73.9	Increased incidence of severe complications, longer hospital stays
Hematological malignancies	50–80	Associated with high mortality (e.g., coexisting tumor lysis syndrome, hemophagocytic lymphohistiocytosis)
Human Immunodeficiency Virus (HIV) infected patients	Risk of mortality 32% higher than in HIV negative patients [3]	Major morbidity and mortality causes; complications from opportunistic infections
Solid organ transplant recipients	7.8–20	Susceptibility to severe infections, extended hospital stays, organ function deterioration

Neutropenia increases the risk of bacterial and fungal infections. Neutrophils may also sustain antimicrobial functional defects resulting in "functional neutropenia" despite preserved cell counts [44–46]. This is often due to chemotherapy or radiation-induced bone marrow failure but can also result from malignant infiltration of the bone marrow. Of note, in a recent meta-analysis on individual data by Georges et al., despite that neutropenia was associated with poor outcome, the association disappeared after granulocyte colony-stimulant factor (G-CSF) therapy [47]. The systemic immunity changes in cancer patients are characterized by the increase of immature and immunosuppressive myeloid cellular populations, lymphopenia, altered function of peripheral T cells, increased frequencies of suppressive lymphocyte populations, $CD4^+$ regulatory T cells and regulatory B-cells, changes in neutrophil to lymphocyte ratio (NLR), among many other [48]. In sepsis neutrophils may have impaired chemotaxis and phagocytosis with promotion of neutrophil extracellular traps (NETs) in their interaction with platelets via the Toll-like 2 (TLR2) and TLR4 receptors, expansion of T regulatory cells, decrease CD4 and CD8 cells, immune exhaustion, and T cell apoptosis [49]. The inflammatory response in sepsis is acute and severe while in cancer patients it is chronic with low-grade inflammation (e.g., NLR is acutely increased in sepsis while less pronounced and chronic in cancer).

Immunosuppression in cancer is a broad term which is complex and poorly understood. In contrast to cancer patients, we can learn from other immunosuppressed patients such as solid organ transplant (SOT) patients where sepsis is also frequent and a common cause of death [50, 51], although less often than with other immunosuppressed states. Two large retrospective analysis, one with about 30,000 ICU patients using the Sepsis-3 definition, and another with 903,816 sepsis hospitalizations (4.4% SOT), found that SOT patients presented a 14.4% lower 28-day mortality and OR 0.83 for hospital mortality (95% Confidence Interval, 0.79–0.87) compared to non-SOT septic patients, suggesting that immunosuppression alone may not always be associated with a worse outcome and other deleterious conditions may coexist [52, 53].

The use of immunosuppressive drugs (e.g., corticosteroids or Bruton's Tyrosine Kinase Inhibitors) is increasingly common in various diseases and in cancer patients. These drugs affect both innate and acquired immunity by diminishing phagocytosis and thereby the killing of bacterial and fungal pathogens, leading to systemic infections and significant defects in cell-mediated immunity during long-term treatment.

Table 2 Risk for specific pathogens according to the type of immunosuppression

Immunologicdeficiency	Neutrophils	Monocytes/dendritic cells/ macrophages	B lymphocytes	T lymphocytes	Humoral (antibody) immunity	Anatomical Compression, obstruction, ulceration
Diseases	Acute leukemia; myelodysplastic syndrome; aplastic anemia; chemotherapy and drug-related neutropenia	Hairy cell leukemia; aplastic anaemia; allogeneic bone marrow transplant; malignant histiocytosis; acute myeloid leukemia; chronic myeloid leukemia; solid tumors; hemophagocytic lymphohistocytosis	Multiple myeloma; B-cell lymphoma; chronic lymphocytic leukemia	T-cell leukemia; T-cell lymphoma; Hodgkin disease	Multiple myeloma; chronic lymphoid leukemia	Solid tumors
Treatments	Chemotherapy induced neutropenia	Steroids; basiliximab; antithymocyte globulin; tacrolimus; mycophenolate mofetil; belatacept	Chemotherapy; steroids; asplenia; rituximab; CAR-T cells; allogeneic bone marrow transplant	Steroids;fludarabine; cyclophosphamide; methotrexate; azathioprine; alemtuzumab;; cyclosporine;mTOR inhibitors (sirolimus);tacrolimus; 2-chlorodeoxyadenosine; daratumumab; allogeneic bone marrow transplant; solid organ transplant	Ibrutinib; rituximab; daratumumab; cyclophosphamide; hypogammaglobunemia induced CAR-T cells; allogeneic bone marrow transplant; solid organ transplant	Chemotherapy-induced neutropenia
Most frequently encountered infections	Gram-negative bacteria Gram-positive bacteria Candida Aspergillus Nocardia	Non-tuberculousmycobacteria Salmonella, Listeria, Legionella, Histoplasma, Brucella Herpes simplex virus, varicella zoster virus, parainfluenzavirus, respiratory syncytial virus Candida parapsilosis Staphylococcus aureus, Enterococcus faecalis, Pseudomonas aeruginosa	Encapsulated bacteria (Streptococcus pneumoniae, Streptococcus pyogenes, Haemophilus influenzae) Giardia lamblia, Campylobacter, Salmonella Mycoplasma Enterovirus Recurrent infections	Herpes simplex virus, Cytomegalovirus, Epstein-Barr virus Pneumocystis, Aspergillus, Cryptococcus Mycobacterial infection Skin candidiasis Diarrhea (rotaviruses, adenoviruses, Cryptosporidium, microsporidia,etc.) John Cunningham (JC) virus	Encapsulated bacteria (S. pneumoniae,S pyogenes, H. influenzae) Mycoplasma, Ureaplasma urealyticum Other infections related to associated T-cell defects	Gram-negative bacteria Gram-positive bacteria

These effects are dose-dependent and worsen with the combination of drugs [54]. Cytotoxic antineoplastic drugs affect all rapidly dividing cells, including bone marrow and gastrointestinal mucosa cells, making mucocutaneous barrier translocation a common source of bacterial infection in cancer patients. Antimetabolite agents (e.g., methotrexate, fluorouracil), often combined with corticosteroids, cause neutropenia and mucositis [55]. Alkylating agents (e.g., cyclophosphamide) cause bone marrow suppression, lower neutrophil, and lymphocyte counts, and increase the risk of infection. Anthracyclines (e.g., doxorubicin) also cause neutropenia and mucositis. Purine analogues (e.g., fludarabine) result in prolonged T-cell lymphopenia, exposing to infection from *Staphylococcus*, *Streptococcus*, GNB, *Listeria*, and *Mycobacteria* [56]. Anti-lymphocyte monoclonal antibodies (e.g., rituximab) deplete B lymphocytes, and alemtuzumab causes prolonged B- and T-cell lymphopenia, leading to a wide range of bacterial and non-bacterial infections [57]. Immune therapies (e.g., Anti-Tumor Necrosis Factor) affect both innate and acquired immune responses to microbial pathogens. Mycophenolate mofetil inhibits lymphocyte clonal expansion upon antigen exposure, while calcineurin inhibitors (cyclosporine and tacrolimus) primarily affect T-cells [58]. Anthracyclines can cause cardiotoxicity and long-term corticosteroid use can cause adrenal insufficiency. Altered gut microbiota diversity secondary to prolonged antimicrobial exposure is also a risk factor for bacteremia [59, 60]. Endothelial stress secondary to cytotoxic chemotherapy could impair vasopressor response, although a study found no increased shock severity in cancer patients from chemotherapy exposure [61].

Evidence that immunosuppression affects severity of sepsis is conflicting and perspectives on the consequences of immunosuppression on the severity of sepsis may be changing. A recent multicenter retrospective study, comparing septic shock in non-cancer patients but on long-term immunosuppressive therapy to patients without immunosuppressive therapy, found no differences in ICU and 3-month mortality [62]. Another study found that in-hospital mortality was lower in patients taking immunosuppressive drugs than in patients not taking immunosuppressive drugs [63]. An experimental porcine study showed that immunosuppression from cyclosporine, methylprednisolone, and mycophenolate did not alter the hemodynamic response in septic shock. Plasma cytokines were similar, except for lower interleukin-6 and higher interleukin-10 levels in the immunosuppressed group [64].

Diagnostic challenges

The early recognition of clinical signs of sepsis is challenging in cancer patients because they may not display the same features as immunocompetent individuals. Corticosteroids can mask fever, whereas lymphoproliferative disorders and chemotherapy (e.g., cytosine arabinoside, dacarbazine, cyclophosphamide) can cause non-infectious fever. White blood cell count can either be high, e.g., after corticosteroids or granulocytic stimulants, or low, e.g., after chemotherapy. Due to a reduced inflammatory response, typical signs like redness, pain, heat, and swelling may be absent [65, 66]. A low neutrophil count in the affected tissues may minimize the signs of infection which may worsen during recovery: e.g., acute respiratory distress syndrome may develop during neutropenia recovery in hematology malignancies with pneumonia [37].

Chest radiography, often first ordered for suspected lower respiratory tract infections, lacks sensitivity and specificity, making it difficult to detect new infiltrates and differentiate infection from inflammation (e.g., drug toxicity, radiation injury). Early chest computerized tomography (CT) has proven more effective than chest radiography [67, 68]. A study found chest radiography of little value for early diagnosis of pulmonary infections on the first day of neutropenic fever, whereas low-dose CT detected pulmonary infiltrates in 80% of fungal pneumonia cases, with sensitivity, specificity, positive, and negative predictive values of 73%, 91%, 62%, and 94%, respectively [69]. However, international guidelines for community- and/or hospital-acquired pneumonias do not make any specific recommendation for patients with cancer [70].

Biomarkers, which present some limitations in the whole septic population, are even more difficult to interpret in cancer patients with sepsis [71]. Their levels are high in infectious and non-infectious conditions, e.g., mucositis, post-chemotherapy bone marrow depression, graft-versus-host disease, or by the tumor itself. C-reactive protein (CRP) is non-specific and may increase in extensive and metastatic cancers (renal, prostate, bladder), or after invasive procedures, radiation, or medications [72]. CRP concentrations are higher in case of neutropenia but its course over time does not depend on the presence of neutropenia [73]. CRP levels decrease in patients treated with tocilizumab, making it unreliable for detecting infections in this situation [74]. Baseline procalcitonin (PCT) levels are high in thyroid medullary carcinoma, lung cancer, and hepatocellular carcinoma, varying with disease stage, and higher in hematological malignancies than in solid tumors [75]. PCT lacks discriminatory value between GPB and GNB infections and between neutropenic and non-neutropenic patients [76].

Pro-adrenomedullin performs better than PCT in hematological patients, and the combination of both biomarkers to the Multinational Association of Supportive Care in Cancer (MASCC) index may be helpful [77]. PCT ≥ 1.5 ng/mL was predictive of septic shock with sensitivity and specificity of 84.0 and 90.7%. A MASCC score < 21 had a 46% sensitivity and 90% specificity in predicting bacteremia, and 68% and 90% in predicting septic shock, respectively [78]. PCT, CRP, and lipopolysaccharide-binding protein did not distinguish between systemic inflammatory response and infection but helped distinguish the presence of bacteremia in neutropenic patients [79]. In a condition of high prevalence of GNB in HSCT recipients, presepsin outperformed PCT and CRP for early diagnosis of GNB bloodstream infections in HSCT [80].

Other conditions that present with fever, multiorgan failure (including shock), and increase in inflammatory biomarker levels can resemble sepsis (Fig. 1). These mimickers include neutropenic enterocolitis (typhlitis), cytokine release syndrome (CRS) after CAR-T cell therapy or bispecific antibodies therapy, tumor lysis syndrome, hemophagocytic lymphohistiocytosis, or engraftment syndrome in HSCT, among others. Differential diagnosis of these syndromes with sepsis/septic shock can be challenging. Neutropenic enterocolitis is a dreadful condition seen after recent chemotherapy. It remains a diagnosis of exclusion that requires histological confirmation [81]. Thus, both clinical and microbiological infections are especially common during severe CRS and associated with poor outcome [82, 83]. Therefore, one should aways entertain the diagnosis of sepsis and initiate immediately empirical antibiotic administration and specific therapy until securing a proper diagnosis.

Management strategies

The management of septic shock in cancer patients should not depart from the strategy recommended for any septic shock and include four tenants: early recognition, early therapy (antibiotics, fluids, vasopressors, and source control), early ICU admission, and adjustment to the presumed cause of septic shock.

Early recognition should include a high degree of suspicion and awareness. The 2021 Surviving Sepsis Campaign guidelines recommend hospitals and health systems implement performance improvement programs, including sepsis screening for acutely ill, high-risk patients, and standard operating procedures for treatment [84]. The 2018 German guidelines for the management of sepsis in neutropenic cancer patients also encouraged screening criteria and performance improvement processes [85]. Many wearable devices such as smartwatches, fitness trackers, and medical devices patched to the body are available in the market. The combination of these devices and anomaly detection models have been used for early detection of COVID-19 infection in ambulatory settings [86]. At the same time, machine learning, artificial neural networks, decision trees, and other techniques have been used to improve early detection and management of sepsis and septic shock [87]. Although in the preliminary stages, their development is rapidly advancing and progressively integrated in our practice as part of the electronic health records clinical decision systems [88].

Early ICU admission is beneficial for septic patients with cancer [89–91]. Delayed ICU admission has been associated with worse outcomes [92, 93]. Criteria alone are neither necessary nor sufficient to offer or decline ICU admission and vary across institutions, culture, and countries. It may be better to assess the potential for ICU admission based on the availability of technical support and clinician expertise. What happens in countries with limited resources is not well known. There is great variability among developing countries according to their size and healthcare systems (e.g., Ecuador versus West Africa-Nigeria or East Africa-Uganda) [94–96], and the availability of sepsis emergency medical services for early recognition, based on clinical signs that are easy to recognize, and simple and clear goal of care [97].

Addressing the suspected or confirmed source of septic shock should account for the type and duration of immunosuppression, prophylaxis given, geographic variations and the prevalence of MDRO, which have had a marked increase worldwide [98]. Recent epidemiologic data on the prevalence of MDRO colonization and infection highlight the role of contact precautions and isolation measures in limiting the emergence of MDRO. The prospective observational CIMDREA study demonstrated that cancer patients had a lower incidence rate of ICU-acquired MDRO colonization and/or infection [99]. Early antibiotic therapy and source control (e.g., removal of infected catheter) are particularly essential among patients with cancer and/or shock. In a study by Mokart et al. in neutropenic patients with severe sepsis, a delay of one hour between the first sign of sepsis in the ICU and the initiation of antibiotics was associated with an odds ratio of death of 10 [100]. In a recent observational study of 273,255 patients with community-onset sepsis, shorter time-to-antibiotics was associated with greater absolute mortality reduction among patients with metastatic cancer [101].

Recommendations for the antimicrobial treatment of neutropenic sepsis are consistent [102–105]. According to the ecology of the hospital, previous antibiotic exposure, and colonization, antibiotic treatment is based upon intravenous anti-pseudomonal cephalosporin or piperacillin-tazobactam or carbapenem. In critically ill patients,

CLINICAL VIGNETTE 1: Septic Shock in Neutropenia

Medical history
72-year-old woman.
Multiple myeloma under treatment with corticosteroids and chemotherapy through a long-term central venous catheter; last chemotherapy was 6 days ago. Her daughter found her altered, cold, and clammy.

Reason for Intensive Care Unit admission
On presentation, she showed sign of dehydration with preserved blood pressure and no fever. WBC count 0.4×10^9/L, CRP 57 mg/L, platelet count 67×10^9/L, creatinine 67 µmol/L (0.76 mg/dL). Initial impression was viral infection, and she went to a general medical floor where she developed hypotension and respiratory failure and transferred to the ICU.

Complementary tests
In the Intensive Care Unit, paired blood cultures were immediately taken from her tunneled central venous device and from a peripheral vein.

Treatment
Fluid resuscitation.
Intravenous broad-spectrum antibiotics (piperacillin-tazobactam).
Granulocyte-colony stimulating factor.
Norepinephrine, and invasive mechanical ventilation.

Evolution in the Intensive Care Unit
Her condition initially worsened, and her antibiotics escalated to meropenem and vancomycin. Blood cultures were positive for Methicillin - resistant *Staphylococcus* from her central venous catheter, which was immediately removed. Follow-up blood cultures were negative. A transesophageal echography did not show any valvular alterations. The patient gradually recovered and weaned off vasopressor and mechanical ventilation within 7 days.

Take home messages
- Neutropenic sepsis is a medical emergency with high mortality. Rapid treatment initiation is essential, as the outcome worsens with every hour passed without relevant treatment.
- However, in many cases (e.g., corticosteroids), the inflammatory response is blunted, rendering the diagnosis of sepsis less obvious. The initial symptoms are often nonspecific, such as confusion or oliguria.
- Therefore, in neutropenic patients receiving treatment for cancer, a high degree of vigilance is necessary.
- The initial management in patients with neutropenic sepsis is identical to non-neutropenic sepsis and should follow the Surviving Sepsis Campaign guidelines.
- In neutropenic sepsis, hematopoietic colony stimulating factors could be considered in sepsis patients with high risk for complications or poor prognostic factors.
- Neutropenia is not associated with mortality in hematological critically ill patients.

CLINICAL VIGNETTE 2: Septic Shock in Hematopoietic Stem Cell Transplantation

Medical history
28-year-old woman.
High-risk acute myeloid leukemia (**AML**) in complete remission after induction and consolidation with chemotherapy.
Admitted to the hospital for allogeneic hematopoietic stem cell transplantation (**HSCT**) from an HLA-compatible donor (brother).
She is receiving graft-versus-host-disease (**GVHD**) prophylaxis with tacrolimus, and antimicrobial prophylaxis with levofloxacin, acyclovir, and fluconazole.

Reason for Intensive Care Unit admission
On day +15 after HSCT, she presents with fever, hypotension (80/40 mmHg) and respiratory failure (respiratory distress and SpO_2/FiO_2 290).

Complementary tests
White blood cell count 0.4×10^9/L, C-Reactive Protein 30 mg/L, platelet count 8×10^9/L creatinine 120 µmol/L (1.36 mg/dL), lactate 6 mmol/L.
Blood cultures and non-invasive analysis of virus and fungi were obtained.

Treatment
Fluid resuscitation.
Intravenous broad-spectrum antibiotics, including antifungal.
Norepinephrine.
High-Flow Nasal Cannula (FiO_2 50%, 40 L/min).

Evolution in the Intensive Care Unit
Positive blood cultures for *Pseudomonas aeruginosa*.
Antibiotics were adjusted according to antibiogram.
The patient gradually recovered and went home 5 days later.

Take home messages
- HSCT leads to extremely immunosuppressed patients that are at substantial risk of life-threatening complications, especially in the first weeks after the transplant.
- Risk of sepsis is high due to the immunosuppression (neutropenia, T cell defects…), as well as mucositis and presence of long-term indwelling catheters, among others.
- Causes of sepsis vary depending on the timing after HSCT.
  - In the first month, bacteria are the most common agents, but sepsis can also be caused by fungi (Candida, Aspergillus), viruses (cytomegalovirus and other herpesvirus can reactivate) and parasites (toxoplasma).
- Differential diagnosis also includes sepsis mimickers such as engraftment syndrome, sinusoidal obstruction syndrome, transfusion reaction, or medication toxicity, among others.
- Reasonable changes in modifiable immunosuppression factors (e.g., GVHD prophylaxis), should be considered in case of life-threatening sepsis.
- The initial management is identical to other sepsis patients and should follow the Surviving Sepsis Campaign guidelines.

CLINICAL VIGNETTE 3: Septic Shock Mimickers

Medical history
54-year-old man
Large B-Cell lymphoma refractory to two lines of chemotherapy
Admitted to the hospital for treatment with CAR T-cell and CD19 therapy.

Reason for ICU admission
After lymphodepletion with fludarabine and cyclophosphamide CAR T-cell was infused (day 0).
On day +2, he developed high fever (without evident source of infection), dyspnea, and hypotension refractory to fluids.

Complementary tests
Neutropenia (white cell count 700 cells/mm^3)
Increased C-reactive protein (180 mg/L)
Blood cultures

Treatment
Broad spectrum antibiotics + acetaminophen (paracetamol)
Supplemental oxygen
Norepinephrine
Tocilizumab (8mg/Kg) and Dexamethasone (10 mg)

Evolution in the ICU
After 24 hours of treatment, fever abated, and the hemodynamics status normalized.
All treatment, including antibiotics, were discontinued on day +5.

Take home messages
- Immunosuppressed patients can present with mimickers of septic shock (hemophagocytic lymphohistiocytosis, tumor lysis syndrome, …)
- Cytokine releasing syndrome (CRS) in CAR T-cell therapy is one of them.
- CRS is a common complication after CAR T-cell therapy. However, all these patients are also at high risk of sepsis, and delayed treatment of sepsis could be fatal.
- The elevated risk of infection, the presence of neutropenia, and the difficult differential diagnosis impose to rule out sepsis first and start empirical antibiotic which can be deescalated or discontinued once the diagnosis of sepsis has been reasonably rule out.

Fig. 1 Clinical vignettes: The need for a prompt admission to the ICU should be addressed for each vignette presented here

a combination therapy associating a beta-lactam with an aminoglycoside is safe [106] and has been associated with lower mortality [20, 28]. Patients previously colonized by Methicillin-resistant *Staphylococcus* or Vancomycin-resistant *Enterococcus* or at elevated risk of carriage by resistant GBP should receive antibiotics that cover them. Vancomycin is the historical drug of choice for the treatment of MRSA, but linezolid, daptomycin and ceftaroline are also safe and efficient in this setting. Depending also on the clinical context, fungal and viral coverage could also be necessary [107]. Timely de-escalation with adequate antibiotics in neutropenic sepsis is safe and appropriate [108].

In the absence of specific data for cancer patients, fluid therapy and vasopressor administration should follow the recommendations for non-cancer patients [109]. A liberal red blood cell transfusion with a hemoglobin trigger of 9 g/dl was no more favorable than a restrictive strategy with a hemoglobin trigger of 7 g/dl in a population that included hematological malignancy and metastatic cancer [110]. However, a single center study in cancer patients with septic shock showed a survival trend favoring a liberal transfusion strategy when applied within the first 6 h of ICU admission [111] and a liberal transfusion strategy was associated with fewer major postoperative complications in patients having major cancer surgery compared with a restrictive strategy [112]. We need more studies to elucidate those discrepancies.

Prevention of infections is critical in high-risk oncology patients, and several organizations have developed evidence-based recommendations for antimicrobial prophylaxis that are beyond the scope of our review [113]. These range from the use of antibiotics (e.g., levofloxacin, trimethoprim/sulfamethoxazole, and cefpodoxime) to prevent bacterial infections in patients receiving treatments that cause neutropenia for over a week to the use of antifungals (e.g., fluconazole, posaconazole, voriconazole) in patients after stem cell transplant, acute myeloid leukemia. Antivirals (e.g., valacyclovir, acyclovir, letermovir, entecavir) are also added in these immunosuppressed groups to prevent herpes simplex, varicella zoster virus, cytomegalovirus, or hepatitis B virus [114].

Outcomes

Mortality in cancer patients with septic shock remains high but has declined over time [30, 115, 116] and may vary according to centers [117, 118] and the immunodeficiency profile [119]. Three factors may be misconstrued as poor outcome: First, the use of Sepsis-3 criteria is associated with higher mortality (patients are sicker); second, there is admission selection bias (only the sicker patients or those expected to survive are admitted); third, cancer has become a chronic disease and more cancers at advanced stages are now admitted to the ICU. In 2019, Hensley et al. reported a 27.9% in-hospital mortality for septic cancer patients versus 19.5% for non-cancer septic patients [2]. A systematic review and meta-analysis by Nazer et al. found a mortality rate of 60% among septic cancer patients [120]. Kim et al. reported that among 322,526 patients hospitalized for septic shock (2009–2017), 13.6% had cancer, with 52% 30-day and 81.2% one-year mortality [121]. Two other studies using Sepsis-3 criteria found high mortality in cancer patients with septic shock [28, 29]. Hematological patients had 67.7% 28-day and 80.6% 90-day mortality, while solid tumor patients had 69.4% and 77.1%, respectively. Studies using older criteria reported lower mortality rates, whereas mortality was higher when using Sepsis-3 definitions [122] (Table 3).

In cancer patients admitted to ICU with septic shock, different predictors have been identified: First, predictors of reduced survival include mechanical ventilation, illness severity, thrombocytopenia, positive cultures, elevated bilirubin, and high lactate level [123]. Increased mortality in hematologic cancer patients was associated with respiratory failure, higher Sequential Organ Failure Assessment (SOFA) score on admission, and high lactate levels [28]. The degree or organ dysfunction and neutropenia were not associated with increased mortality [124, 125]. In solid tumor patients, mortality predictors included high lactate levels, metastatic stage, respiratory failure, and an Eastern Cooperative Oncology Group (ECOG) score of 3 or 4 [29]. Second, predictors of improved survival in hematological patients include higher albumin levels, the use of aminoglycoside, and G-CSF [28].

Reluctancy to ICU admission stems from the fact that the mortality in cancer patients admitted to the ICU with septic shock can be exceedingly high, raising questions about aligning ICU admission with goals of care and the decision to forgo life-sustaining therapy [28, 29, 126]. Recently, a study on the prognosis of patients with septic shock compared those with and without cancer and showed no difference, which is a similar ICU and hospital mortality [107]. A new paradigm is that ICU admission should not depend on the underlying immunosuppression and stage of cancer but on the degree of clinician expertise, technological support readily available and multi-discipline collaboration including telemedicine [127].

Besides the common determinants of death related to the underlying functional impairment and the extent of organ dysfunction, therapeutic strategies associated with improved survival include early recognition, early adequate antibiotic therapy and source control, early ICU admission. More debated issues are the inclusion of

Table 3 Studies reporting mortality in cancer patients with septic shock comprising study populations since 2004

Ref	Year	Country	N	Cancer type(s)	Mortality				
					28–30 day	90-day	In-hospital	In-ICU	1-year
[140]	2024	USA	132	Solid: 50%HM: 50%	80 (60.6)			57 (43.2)	110 (83.3)
[141]	2022	Korea	897	Solid	237 (26.4)[1]				
[121, 142]	2022	Korea	43,466	Solid: 87.7% HM[2]: 12.3%	22,639 (52.1)				35,338 (81.3)
[29]	2022	USA	271	Solid	188 (69.4)		186 (68.6)	159 (58.7)	
[28]	2022	USA	459	HM	311 (67.8)	370 (80.6)	339 (73.9)	293 (63.8)	
[123, 143]	2021	Jordan	1408	Solid: 67.8% HM: 32.2%			914 (64.9)	688 (48.9)	
[126]	2020	France	252	Solid: 52.8% HM: 47.2%	121 (48)			101 (40)	
[144]	2020	Korea	897	Solid	237 (26.4)				
[149]	2019	Korea	478	Solid		208 (43.5)			
[145]	2019	Saudi Arabia	100	Solid: 68% HM: 32%			76 (76)	61 (61)	
[150]	2019	Taiwan	11,825	Solid			8199 (69.3)		
[146]	2018	France	60	Solid: 35% HM: 65%	28 (47)				
[117]	2012	France	3437	Solid: 61.6% HM: 38.3%				2029 (59)	
[147]	2011	Mexico	82	Solid: 68% HM: 32%				34 (41.5)	
[115]	2008	France	148	Solid: 42.6% HM: 57.4%	78 (52.7)				
[148]	2008	Korea	50	HM				30 (60)	

[1] Number (%); [2]Hematological cancer, *HM* Hematological, *ICU* Intensive Care Unit

aminoglycosides, the place of liberal blood transfusion, and the addition of colony-stimulating factors [128, 129].

It is important to note that evaluating the prognosis of cancer patients may require different criteria than those for non-cancer counterparts. Emphasis on hospital discharge and quality of life may be more appropriate measures in advanced cases not responding to cancer therapies [130]. Additionally, assessing the risk of ICU readmission and further adjusting the underlying hematology-oncology management, such as reducing therapy intensity, discontinuing treatment, and emphasizing patient-centered palliative care are also important considerations [131, 132].

Gaps and future research directions

Because of their exclusion from epidemiological studies and clinical trials, the management of cancer patients follows the rules established for non-cancer patients. Efforts should be made to include more diverse populations in clinical trials to reduce the inappropriate extrapolation of potentially inapplicable results to underrepresented patient groups [133]. Poor clinical outcomes may be due to delay in therapy, inadequate therapy, or simply lack of data available regarding specific interventions in this population, rather than the shortfalls in medical care or healthcare systems.

Research priorities should include developing better diagnostic and prediction tools (e.g., use of artificial intelligence), better understanding of the pathophysiology of critical illness in cancer patients, optimizing diagnostic strategies, role of new immunotherapy agents (e.g., checkpoint inhibitors), treatment protocols (e.g., integration of machine learning models) [134, 135] and new challenges for palliative care such as dealing with novel side effect profiles and coping with greater uncertainty regarding prognosis [132]. Identifying prognostic factors in addition to patient age, cancer type, disease stage, and prior treatment responses is also crucial for guiding ICU decisions and improving patient outcomes [109].

Implications for clinical practice and recommendations

Strategies to identify these patients early and application of unbiased ICU admission criteria are crucial for improving clinical outcomes [136, 137]. Triage decisions should be based on intensive care needs rather than the malignancy or immunosuppression alone, and the management supported by a multidisciplinary team approach to provide comprehensive care. We propose a ***new***

paradigm that integrates innovative technologies and practices across the healthcare continuum of these complex patients (Fig. 2). An integrated system where risk assessment, active surveillance (e.g., wearable technologies), accurate sepsis prediction models through machine learning and artificial intelligence, precision medicine (e.g., metabolomics, proteomics), and others will complement the targeted management strategies [138].

To improve outcomes for cancer patients, it is crucial to promote awareness of the detrimental effects of failing to control infections in their initial stages. Developing strategies for earlier detection and avoiding misdiagnosis with non-infectious causes is essential. Early interventions by critical care teams, such as through critical care outreach programs, early warning systems, remote tele-ICU particularly when specialized ICU beds are sparse, and earlier admission to ICU, improve outcomes. Adequate management of antimicrobials is essential. Additionally, there is a need for more research into the ambulatory antimicrobial management of these patients, as well as further investigation into the accuracy of biomarkers and phenotype profile, the combined use of aminoglycosides, e.g., Combination-Lock01 study [139], the role of hematopoietic colony stimulating factors in cases of neutropenic sepsis or septic shock and optimal blood transfusion strategy.

Conclusion

Cancer incidence rates are rising, and so are the rates of septic shock among these patient populations. Malignancies are risk factors for sepsis and septic shock due to their impact on both innate and acquired immunity. Infection symptoms in cancer patients may be lacking, necessitating a high index of suspicion and early

Surveillance
Use of wearable devices in the outpatient environment, outreach programs, other electronic surveillance systems
Early Recognition
Use of wireless technologies, artificial intelligence, novel biomarkers, early use of advance imaging
Medical Informatics
Integration of machine learning models into clinical practice, integration of artificial intelligence in the healthcare system
Early Intervention
Early antimicrobial therapy, antimicrobial prophylaxis, use of Granulocytes Colony Stimulant Therapy, other
Precision Medicine
Use of pharmaco-genomic biomarkers, metabolome, proteome, and others to tailor sepsis management
Comprehensive Management Strategies
Multidisciplinary approach, consideration of microbiome, and other
Risk Assessment and Prognostic Indicators
Use of novel biomarkers and mathematical models to predict risk of bacteremia, clinical deterioration, and survival
Integration of Supportive Care and Palliative Care
Strong focus on quality of life, discharge planning
New Paradigm

Fig. 2 New Paradigm. Despite a rise in prevalence and severity of septic shock in immunosuppressed patients, survival has improved over time. An advanced stage of the disease should not deter from ICU admission, nor the use of novel technologies such as wearable devices, outreach programs, artificial intelligence, and machine learning models for early detection and diagnosis. Critical care should remain in line with values and preference of the patient supported by their family

detection through more accurate and rapid methods. The sites of infections often depend on the cancer type. The types of organisms vary based on the type of immunosuppression, disease stage, duration, therapies, and local prevalence of MDRO. Mimickers of septic shock should always be on the differential. While cancers can be risk factors for poor outcomes, immunosuppressive therapies or immunotherapies might mitigate the immune response which deserves further investigation.

Septic shock is a medical emergency which imposes an immediate transfer to the ICU when there is a need for specific technical support and critical care expertise. Management of septic shock in immunosuppressed cancer patients should follow general sepsis management guidelines with additional considerations tailored to specifics inherent to cancers. Understanding and addressing the unique needs of cancer patients through a new paradigm, which includes the integration of innovative technologies into our healthcare system, targeted management strategies, and robust clinical practices, including early identification and diagnosis, coupled with early admission to ICUs that promote a multidisciplinary approach, is crucial for improving their prognosis and overall survival rates. No cancer patient should eschew ICU care solely because of their underlying disease.

Abbreviations

CRP	C- reactive protein
CRS	Cytokine release syndrome
CT	Computerized tomography
ECOG	Eastern Cooperative Oncology Group
ER	Emergency room
G-CSF	Granulocyte colony stimulating factor
GNB	Gram-negative bacteria
GPB	Gram-positive bacteria
HSCT	Hematopoietic stem cell transplantation
ICU	Intensive Care Unit
MDRO	Multidrug-resistant organisms
NET	Neutrophil extracellular trap
NLR	Neutrophil to lymphocyte ratio
PCT	Procalcitonin
SOT	Solid organ transplantation

Author contributions

All authors collaborated to the conception of the manuscript, the redaction of the draft, tables and figures, editing and final approval of the manuscript. J.L.N. and P.R.B. put the manuscript together, and harmonized flow and balance of the whole project.

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